REMARKS/ARGUMENTS

Claims 4, 6-10, 12-15 and 17-18 are pending in this application and presented for examination. Claims 17 and 18 are allowable. Claim 4 has been amended to more clearly set forth the claimed invention. Claims 8-10 and 12-15 contain allowable subject matter. No new matter has been entered with the foregoing amendment. Reconsideration is respectfully requested.

I. THE INVENTION

The present invention is directed to a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative. The ionic compound is capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative. Unexpectedly, these ionic complexes exhibit an excellent sustained release effect.

II. FORMALITIES

Applicants submitted an Information Disclosure Statement on June 23, 2000. To date, the initialed copy of Form PTO-1449 was not returned. Applicants submit herewith a new copy of previously submitted Information Disclosure Statement and Form PTO-1449 and respectfully request that the Examiner initial the same and return it to the undersigned representative.

III. REJECTION UNDER 35 U.S.C. § 102

The Examiner has rejected claims 4 and 7 as allegedly being anticipated by Hirano, *et al.* The Examiner states that Hirano, *et al.* teach a compound of instant formula I, which is administered to dogs and then excreted in their urine. The Examiner alleges that the

dog's urine would contain ionic compounds. In response, Applicants respectfully traverse the rejection.

As the Examiner is well aware, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. M.P.E.P. § 2131.

Hirano, *et al.* disclose the excretion and metabolism of beraprost sodium in dog, but do not disclose or suggest a ***sustained release pharmaceutical composition*** comprising the elements of an *ionic* prostaglandin I_2 derivative *and* an ionic compound having an opposite charge to that of the ionic prostaglandin I_2 derivative. In fact, Hirano, *et al.* do not disclose or suggest any pharmaceutical composition. As Hirano, *et al.* do not disclose or even suggest each and every element of the sustained release pharmaceutical composition of claim 4, Hirano, *et al.* do not properly anticipate claim 4 or dependent claim 7.

Moreover, as is presently taught and claimed, in order to further increase the hydrophobicity of the pharmaceutically active substance accompanied by the formation of the ionic complex, it has been found that depending upon the kind of the cationic compound, there is a difference in the octanol/water partition coefficient of the anionic prostanoic acid derivative associated with the ionic complex. A better sustained release effect is obtained with a larger coefficient. (please see page 6, lines 7-18). This cationic compound, which increases the octanol/water partition coefficient, is neither taught nor suggested by Hirano, *et al.*

In addition, even if the dog urine as disclosed in Hirano, *et al.* contains a ionic compound of opposite charge, and Applicants maintain there is no such teaching, there is no teaching or even a suggestion of disclosing an amount sufficient to increase the octanol/water coefficient.

Claim 4 recites a sustained release ***pharmaceutical composition*** comprising an ionic prostaglandin I_2 derivative *and* an ionic compound having an opposite charge to that of the ionic prostaglandin I_2 derivative. Dog urine is not a sustained release ***pharmaceutical composition.*** The pharmaceutical compositions of the present invention are satisfactory for ***clinical use***. (please see page 5, lines 13-16). Dog urine is in no way suitable for ***clinical use.*** Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. REJECTION UNDER 35 U.S.C. § 103

The Examiner has rejected claim 6 as allegedly being obvious over Hirano, *et al.* The Examiner states that Hirano, *et al.* teach a compound of instant formula I, which is administered to dogs and then excreted in their urine. The Examiner alleges that claim 6 embodies mere optimization of the composition's ingredients and therefore, claim 6 is obvious in view of Hirano, *et al.* In response, Applicants respectfully traverse the rejection.

The pharmaceutical compositions of the present invention, especially those having large partition coefficients have sustained release effects, are far superior to the prostanoic acid derivatives alone. An excellent sustained release composition is obtained by increasing the hydrophobicity of the prostanoic acid derivative. The ionic compound is capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative. Unexpectedly, these ionic complexes exhibit an excellent sustained release effect.

These unexpected advantageous properties are sufficient to rebut any *prima facie* case of obviousness. Again, ***even if*** the dog urine as disclosed in Hirano, *et al.* contains a ionic compound of opposite charge, and Applicants maintain there is no such teaching, there is no teaching or even a suggestion of an amount sufficient to increase the octanol/water coefficient. The ionic compound enhances the hydrophobic property of the ionic prostanoic acid derivative such that the ionic complexes exhibit an excellent sustained release effect.

Applicants can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillion*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990). The following argument was presented in Applicants' response dated August 13, 2002.

Applicants maintain that a *prima facie* case of obviousness has not been established. However, the comparative data filed with the application rebuts any *prima facie* case of obviousness. The Examiner's attention is respectfully directed to Table 1 on pages 24-25 of the disclosure. As shown therein, an increase in the partition coefficient of the ionic prostanoic acid derivative was noted with alkylbenzylammonium salts such as tributylbenzylammonium chloride, alkyltrimethylammonium salts such as

lauryltrimethylammonium chloride, lidocaine hydrochloride and meprylcaine hydrochloride. Results reveal that the compounds having opposite charges such as quaternary ammonium or phosphonium groups and highly hydrophobic substituents exhibit the effect of increasing the hydrophobic property of the ionic prostanoic acid derivative (*see*, page 25, lines 24 -28 of the specification).

However, inorganic salts such as magnesium chloride or arginine hydrochloride, failed to enhance the hydrophobic property of beraprost sodium (BPS) (*see*, page 23, lines 19-23). Thus, no increase in the partition coefficient was noted.

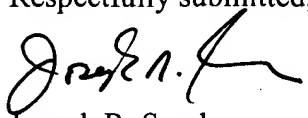
Further, the Examiner attention is respectfully directed to page 29, bridging to page 30 and Figure 3. As explained in Test 5, inventive Example 17 and comparative Example 4 were administered to Winstar rats. As shown in Figure 3, the inventive composition 17 (closed circles) showed a sustained released compared to the comparative Example 4 (open squares). Thus, the compositions as presently claimed produce unexpectedly improved properties for controlled release. These unexpected advantageous properties represent objective evidence sufficient to rebut a *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection.

V. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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